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Lockwood G. Taylor

US Food and Drug Administration, lockwood.taylor@fda.hhs.gov

Steven T. Bird

US Food and Drug Administration

Leyla Sahin

US Food and Drug Administration

Melissa S. Tassinari

US Food and Drug Administration

Patty Greene

US Food and Drug Administration

See next page for additional authors

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Authors

Lockwood G. Taylor, Steven T. Bird, Leyla Sahin, Melissa S. Tassinari, Patty Greene, Marsha E. Reichman, Susan E. Andrade, Katherine Haffenreffer, and Sengwee Toh

BRIEF REPORT

Antiemetic use among pregnant women in the United States: the escalating use of ondansetron

Lockwood G. Taylor^{1*} , Steven T. Bird¹, Leyla Sahin¹, Melissa S. Tassinari¹, Patty Greene¹, Marsha E. Reichman¹, Susan E. Andrade², Katherine Haffner³ and Sengwee Toh³

¹Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

²Meyers Primary Care Institute (Fallon Community Health Plan, Reliant Medical Group, and University of Massachusetts Medical School), Worcester, MA, USA

³Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

ABSTRACT

Purpose To examine ondansetron use in pregnancy in the context of other antiemetic use among a large insured United States population of women delivering live births.

Methods We assessed ondansetron and other antiemetic use among pregnant women delivering live births between 2001 and 2015 in 15 data partners contributing data to the Mini-Sentinel Distributed Database. We identified live birth pregnancies using a validated algorithm, and all forms of ondansetron and other available antiemetics were identified using National Drug Codes or procedure codes. We assessed the prevalence of antiemetic use by trimester, calendar year, and formulation.

Results In over 2.3 million pregnancies, the prevalence of ondansetron, promethazine, metoclopramide, or doxylamine/pyridoxine use anytime in pregnancy was 15.2, 10.3, 4.0, and 0.4%, respectively. Ondansetron use increased from <1% of pregnancies in 2001 to 22.2% in 2014, with much of the increase attributable to oral ondansetron beginning in 2006. Promethazine and metoclopramide use increased modestly between 2001 (13.8%, 3.2%) and 2006 (16.0%, 6.0%) but decreased annually through 2014 (8.0%, 3.2%). Doxylamine/pyridoxine, approved for management of nausea and vomiting in pregnancy in 2013, was used in 1.8% of pregnancies in 2014. For all antiemetics, use was highest in the first trimester.

Conclusions We observed a marked increase in ondansetron use by study year, prescribed to nearly one-quarter of insured pregnant women in 2014, occurring in conjunction with decreased use of promethazine and metoclopramide. Given the widespread use of ondansetron in pregnancy, data establishing product efficacy and methodologically rigorous evaluation of post-marketing safety are needed. Published 2017. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS—antiemetic use; ondansetron; pregnancy; Sentinel

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INTRODUCTION

Nausea and vomiting in pregnancy (NVP) affects up to 80% of pregnant women, predominantly between 5 and 18 weeks gestation.¹ An extreme form of NVP, hyperemesis gravidarum, presents as persistent nausea and vomiting, dehydration, weight loss, and electrolyte abnormalities.¹ Hyperemesis gravidarum

occurs in <3% of pregnancies, can adversely affect both the fetus and mother, and it is the most common reason for first trimester hospitalization.² A systematic review found that women with hyperemesis gravidarum have a higher incidence of low birth weight, premature births, and small for gestational age infants.³

Antiemetic pharmacotherapy has long since played a role in NVP treatment. Metoclopramide, anticholinergics, and 5-hydroxytryptamine-3 antagonist are prescribed off-label for NVP; however, doxylamine/pyridoxine (Diclegis), approved in 2013, is the only medication approved for the treatment NVP.

Ondansetron is a 5-hydroxytryptamine-3 antagonist widely used for the prevention of nausea and vomiting

*Correspondence to: L. G. Taylor, Center for Drug Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Avenue, Bldg 22, Rm 2406, Silver Spring, MD 20903, USA. E-mail: lockwood.taylor@fda.hhs.gov

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associated with chemotherapy, radiotherapy, and in postoperative settings. While ondansetron is not approved for NVP, it has been prescribed off-label for the condition. Recent studies have suggested possible ondansetron-associated birth defects with use during the first trimester of pregnancy,^{4,5} but evidence to date is limited and inconclusive. We sought to evaluate the extent of ondansetron use in pregnancy, in the context of other antiemetic use, among a large insured US population of women delivering live births.

METHODS

Data sources

The Mini-Sentinel pilot was launched in 2009 by the US Food and Drug Administration (FDA) to perform active surveillance for medical product safety.⁶ Briefly, Mini-Sentinel consists of electronic healthcare data from a distributed network of 18 data partners, mostly large commercial health insurers, who contribute data using a common data model. The common data model allows for standardized queries across data partners and includes a robust data quality assurance process.⁷ This analysis included the 15 data partners (14 private [e.g., Aetna, Humana] and one public insurer [Tennessee Medicaid]) that contributed data on pregnancies including inpatient, outpatient, and emergency room diagnoses and procedures, outpatient pharmacy dispensing, and demographic and healthcare enrollment between April 2001 and October 2015. Not all data partners contributed data over the entire study period, with more partners contributing data in more recent years (Table S1).

Pregnancy identification

Pregnancies ending in live births among women aged 10 through 54 years at delivery were identified using a validated algorithm based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes.⁸ Eligible women required continuous medical and pharmacy healthcare enrollment for a minimum 480 days prior to delivery admission to capture drug exposures during and prior to pregnancy.

Drug exposure

Use of the following antiemetics among pregnant women was identified using National Drug Codes: dolasetron mesylate (injectable, oral), doxylamine succinate/pyridoxine (oral), granisetron (injectable, oral, transdermal), metoclopramide (injectable, oral),

ondansetron (injectable, oral), palonosetron (injectable), prochlorperazine (injectable, oral, rectal), and promethazine (injectable, oral, rectal). Pregnant women were considered exposed if they received at least one antiemetic (dispensed or administered) anytime during pregnancy. Trimesters were defined as 0–90 days (first trimester), 91–180 days (second trimester), and 181 through the delivery date (third trimester).

Data analysis

Each site submitted aggregate-level data to the Mini-Sentinel Operations Center to create overall estimates of antiemetic use by formulation, trimester, maternal age, and calendar year. Analyses of antiemetic use by year excludes 2015 because this was a partial year of data, and not all data partners contributed data for this year at the time of the data pull. Trend analyses evaluated the change in the percent utilization by calendar year rather than the absolute number of users per calendar year to account for the fact that not all data partners contributed data over the entire study period. Analyses were conducted using SAS 9.3 (Cary, North Carolina). No individual-level data were transferred to the Mini-Sentinel Operations Center or the US FDA. Mini-Sentinel projects are classified as public health activities, and individual Institutional Review Board approval was not required.⁹

RESULTS

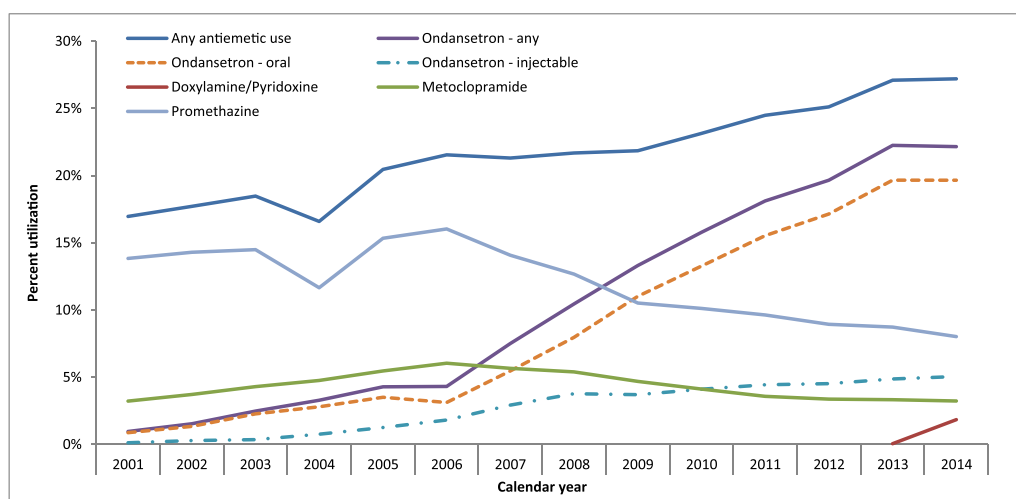
The final sample consisted of 1 949 201 women contributing 2 342 489 live birth pregnancies. Five larger data partners contributed approximately 80% of the data. Population characteristics are shown in Table 1. Over half (54.9%) of the pregnancies were in women at least 30 years of age (Table S2).

During the study period, prescription antiemetic use occurred in 23.5% of pregnancies ending in a live birth. Ondansetron was the most commonly used antiemetic during pregnancy (15.2%), followed by promethazine (10.3%) and metoclopramide (4.0%) (Table 1). For all antiemetics, use was most common in the first trimester and decreased throughout pregnancy.

Any antiemetic use increased from 17.0% of live birth pregnancies in 2001 to 27.2% in 2014. Specifically, ondansetron use in pregnancy increased from 0.96% of pregnancies in 2001 to 22.2% of pregnancies in 2014, with the most substantial increased trend beginning in 2006 (Figure 1). The trend for ondansetron was relatively similar across all data partners contributing data to this analysis (data not

Table 1. Prevalence of antiemetic prescription among live birth pregnancies identified in the Mini-Sentinel Distributed Database, 2001–2015¹

Generic name ²	Use in the 90 days before pregnancy	Any use during pregnancy	Any use, first trimester	Any use, second trimester	Any use, third trimester	Use in first, second, and third trimester
No. pregnancies	<i>n</i> = 2,342,489	<i>n</i> = 2,342,489	<i>n</i> = 2,342,489	<i>n</i> = 2,342,489	<i>n</i> = 2,341,992 ⁴	<i>n</i> = 2,341,992 ⁴
Any antiemetic	78 770 (3.36%)	550 335 (23.49%)	390 217 (16.66%)	265 820 (11.35%)	157 217 (6.71%)	52 453 (2.24%)
<i>Dolasetron</i>	346 (0.01%)	3155 (0.13%)	2167 (0.09%)	1568 (0.07%)	578 (0.02%)	165 (0.01%)
<i>Doxylamine/Pyridoxine</i> ³	30 (0.00%)	8735 (0.37%)	6812 (0.29%)	5943 (0.25%)	1903 (0.08%)	1006 (0.04%)
<i>Granisetron</i>	161 (0.01%)	352 (0.02%)	163 (0.01%)	133 (0.01%)	123 (0.01%)	10 (0.00%)
<i>Metoclopramide</i>	9797 (0.42%)	93 481 (3.99%)	57 433 (2.45%)	38 868 (1.66%)	21 615 (0.92%)	2250 (0.10%)
<i>Ondansetron</i>	39 775 (1.70%)	356 777 (15.23%)	255 825 (10.92%)	167 490 (7.15%)	90 549 (3.87%)	29 390 (1.25%)
<i>Palonosetron</i>	26 (0.00%)	101 (0.00%)	16 (0.00%)	55 (0.00%)	74 (0.00%)	2 (0.00%)
<i>Prochlorperazine</i>	3173 (0.14%)	16 500 (0.70%)	10 263 (0.44%)	6070 (0.26%)	2719 (0.12%)	185 (0.01%)
<i>Promethazine</i>	37 115 (1.58%)	240 748 (10.28%)	158 275 (6.76%)	92 380 (3.94%)	63 774 (2.72%)	13 266 (0.57%)

¹Not all Mini-Sentinel data partners contributed data for the entire study period; 2015 represents partial year of data.²All formulations included (injectable, oral, rectal).³Approved in 2013.⁴Total number of pregnancies is lower for third trimester exposure because some live births occurred in late the second trimester.

* Dashed lines for oral and injection ondansetron form represent a portion of all total ondansetron use as shown by the solid purple line. Summation of oral and injection utilization sums to greater than total ondansetron use since some women received both products.
^a Not all Mini-Sentinel data partners contributed data for the entire study period.

Figure 1. Utilization of antiemetic drugs among live birth pregnancies, by calendar year, in the Mini-Sentinel Distributed Database, 2001–2014^{a,b} [Color figure can be viewed at wileyonlinelibrary.com]

shown). Promethazine use increased modestly between 2001 (13.8%) and 2006 (16.0%) but decreased annually after 2006 to 8.0% in 2014. A similar trend was observed with metoclopramide, with the highest use in 2006 (6.0%), decreasing annually to 3.2% in 2014. Doxylamine/pyridoxine use increased from <0.1% of pregnancies in 2001 to 1.8% in 2014.

Use of both oral and injectable forms of ondansetron increased during the study period (Figure 1; dashed lines). Oral ondansetron use accounted for much of the overall increase in use from 2006 to 2014, during which the prevalence increased six-fold from 3.1 to 19.7%, while the increase in the injectable form was more modest (2006: 1.8%; 2014: 5.1%; some women received both formulations).

DISCUSSION

Our data show ondansetron utilization during pregnancy increased from approximately 1% of all pregnancies in 2001 to nearly a quarter of pregnancies in 2014. The increased trend for ondansetron was observed across all data partners. The marked increase in ondansetron use from 2006 to 2014 occurred in conjunction with decreased use of promethazine and metoclopramide; however, the increase in ondansetron use was significantly higher than the decrease of the latter antiemetics.

While the factors driving the dramatic increase in ondansetron use are unclear, it may in part be explained by the large number of approved generic applications

beginning in 2006 (26 generic applications approved for the oral formulation and 35 applications for the injectable formulation between 2006 and 2015), which may have lowered the cost of ondansetron as well as the potential for relaxed prior authorization policies for reimbursement when prescribed during pregnancy in some health care systems.

Despite the increase in ondansetron utilization, safety and efficacy in pregnancy have not been established. The effective nature of ondansetron for NV post-chemotherapy and radiotherapy has likely facilitated frequent use of this product for NVP; however, ondansetron is not FDA approved for NVP. Ondansetron's safety profile for NVP in the post-marketing setting is conflicting. Two population-based studies have reported positive associations between first trimester ondansetron exposure and cleft palate⁴ and cardiac anomalies⁵, while three other studies^{10–12} found no increase in congenital anomalies. The totality of these studies is not sufficient for definitive conclusions on fetal safety of ondansetron in pregnancy.

A major strength of this analysis is the large number of pregnancies identified to assess medication use. The study population was geographically and demographically diverse. One limitation is that antiemetic use was based on pharmacy dispensing data and not actual use; thus, compliance with oral formulations cannot be assessed. Moreover, because we were unable to capture inpatient oral use of ondansetron in our analysis, total inpatient use of ondansetron during pregnancy may be under-captured which could underestimate the overall use. We cannot confirm whether other precipitating factors, such as gastrointestinal conditions or a history of dehydration, contributed to the decision to prescribe ondansetron. There may have been misclassification of timing of exposure due to estimation of gestational age, although previous studies have demonstrated that claims-based algorithms to obtain gestational age among live births are generally valid.⁸ Also, the study population was limited to predominantly commercially insured women with a live birth delivery; thus, we cannot generalize results to publically insured women as well as to pregnancies not ending in live birth. Finally, we cannot measure whether characteristics of women in the included data partners changed over time, whether formularies changed over time, or whether either of these impacted the utilization curves. However, this would not be expected to greatly affect the trend post 2009 given that nearly all data partners contributed.

The American College of Obstetricians and Gynecologists recommends doxylamine/pyridoxine as first-line pharmacotherapy for NVP.¹³ Early

treatment is recommended to prevent progression to hyperemesis gravidarum. Our data show, in current practice, nearly one-quarter of insured women in Mini-Sentinel received ondansetron during pregnancy, with most usage consisting of oral administration. Given the widespread use of ondansetron in pregnancy, a great need exists for data establishing its efficacy as well as methodologically rigorous post-marketing assessments to evaluate its safety in pregnant women.

KEY POINTS

- Ondansetron use in pregnancy increased markedly over the study period to nearly one in four pregnancies in 2014.
- This off-label use continues despite the approval of another antiemetic for nausea and vomiting in pregnancy and questions surrounding the fetal safety of ondansetron.
- Given the widespread use of ondansetron in pregnancy, a great need exists for rigorous post-marketing studies evaluating its safety during pregnancy.

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ETHICS STATEMENT

Mini-Sentinel projects are classified as public health activities, and individual Institutional Review Board approval was not required.

CONFLICT OF INTEREST

Dr. Andrade has received grant support from Pfizer, Inc.

The authors have no other conflicts of interest to disclose.

This work represents the opinions of the authors and not necessarily that of the Food and Drug Administration.

Authorship

All authors provided (i) substantial contributions to conception or design of the work, or the acquisition,

analysis, or interpretation of data for the work; and (ii) drafting of the work or revising it critically for important intellectual content; and (iii) final approval of the version to be published; and (iv) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data

We thank all of the data partners who contributed data to this study. We are indebted to the Tennessee Bureau of TennCare of the Department of Finance and Administration which provided data.

Data Access, Responsibility, and Analysis

Sengwee Toh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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